REMARKS

Claims 1-26 and 30-31 are currently pending in the application. By this amendment, claims 1, 6, 14, 17, 21, 30 and 31 have been amended. The foregoing separate sheets marked as "Listing of Claims" show all the claims in the application, with an indication of the current status of each.

Claim Objections: 35 USC § 101

Examiner has objected to claim 1 due to the presence of a period following the status identifier. Claim 1 has hereby been amended to delete the period, thereby addressing and overcoming Examiner's objection. In view of the foregoing, Applicant respectfully requests withdrawal of this objection.

Claim Rejections: 35 USC § 112

Claims 1-13, 17-18, 21-22 and 30-31 stand rejected under 35 USC §112, second paragraph, ostensibly due to being indefinite. In particular, Examiner states that claims 1, 6, 30 and 31 recite the phrase "relative ratios" without specifying the type of ratio (e.g. concentration, volume or weight). The independent claims of the rejected group of claims (claims 1, 6, 17, 21, 30 and 31) have hereby been amended to recite that it is the relative ratios of the *amount* of the remaining agents that stays the same in the reduced ray design as in the full ray design. Support for this amendment is found in the specification, for example, on page 13 at lines 20-21.

Claims 1, 6, 21, 30 and 31 are rejected due to the recitation of "algebraic manipulations relating to full and reduced ray mixture models". Claims 1, 6, 21, 30 and 31 are hereby amended to recite that step f involves determining whether or not the remaining agents interact with the subset of agents by utilizing *statistical hypothesis testing* using the full and reduced ray mixture models, in order to detect, characterize or predict an outcome caused by exposure to the agents in the group or mixture. Support for this amendment is found in the specification, for example, on page 18 at lines 9-11, where the use of statistical hypothesis testing is described. Further, throughout the specification, reference is made to various statistical hypothesis when full and reduced ray data is analyzed, e.g. in the figure legends for Figures 3, 6, 11, 12, 15, etc. Applicant

submits that such hypotheses were either known in the art at the time the present application was filed, or described and/or illustrated in the specification as filed, or both.

Claims 2 and 7 stand rejected due to the recitation of "said method" when referring to claims 1 and 6, respectively, whereas, according to the Examiner, more than one method is recited in claims 1 and 6. Claims 1 and 6 have hereby been amended as described in the previous paragraph to remove the word "method", thus making moot this portion of the rejection.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Claim Rejections: 35 USC § 102(b)

Claim 14 stands rejected under 35 USC § 102(b) as anticipated by Gennings et al., (hereafter "Gennings 1997", *Journal of Agriculture, Biological and Environmental Statistics*, 1997, vol. 2, pages 198-211). This rejection is traversed.

General observations concerning the Examiner's comments

The Examiner appears to have a fundamental misunderstanding of the term "Interaction threshold". Applicant refers Examiner to page 19, lines 25-31 and page 20, lines 1-3 of the present application, where the interaction threshold is discussed. A more detailed discussion is presented in Example 8, entitled "Analysis of an Interaction Threshold in a Mixture of Drugs and/or Chemicals", which at page 165 and lines 9-21 states the following:

"The isobologram of Gessner and Cabana (Figure 1) associated with the empirical ED50's of ethanol and chloral hydrate is consistent with the existence of an interaction threshold. Note that the mixture appears to be additive at the 50% level of response for chloral hydrate less than 125 mg/kg and ethanol greater than 1200 mg/kg. When chloral hydrate exceeds 125 mg/kg and ethanol is less than 1200 mg/kg, there is a synergistic interaction. This suggests the possibility of an interaction threshold when the drugs are combined.

The boundary that separates the dose space into regions of interaction and additivity is of interest to locate. The development and subsequent analysis of a model that accommodates the elucidation of the boundary of the two regions is the objective of this report. The interaction threshold boundary may take a variety of different shapes, and the shape of this boundary is not likely to be known. Our goal is to develop a general procedure to accommodate various potential shapes for this boundary."

Applicant notes that, for purposes of the present application, the term "interaction" has a specific meaning as presented in the first sentence of Example 8: "A major task when studying chemical mixtures is to determine whether departures from additivity, i.e. interactions, among the chemicals in the mixture exist." Thus, as used in the present application "interactions" are departures from additivity, and the "interaction threshold" or "interaction threshold boundary" is the "boundary that separates the dose space into regions of interaction [non-additivity] and additivity" as stated in the passage quoted above.

In order to clarify this distinction and to eliminate confusion, claim 14 has hereby been amended to recite "interaction threshold boundary" rather than "interaction threshold". Applicant submits that this amendment does not add any new matter, being fully supported in the passage quoted above, and is made for the purpose of highlighting a salient feature of the invention but not in any way narrowing the claim scope.

No such concept is present in Gennings 1997. Rather, Gennings 1997 describes a "threshold additivity model". The concept of "threshold" is defined in the first paragraph, which states: "These response mechanisms suggest the existence of thresholds, or *exposure levels below which the background response results*, while levels exceeding the threshold result in a 'dose-response' trend". Thus, "threshold", as used in this article, refers to exposure levels of mixtures of chemicals below which a "background" response results (i.e. a response associated with zero exposure levels) and above which a response can be detected. Applicant notes that this threshold does not distinguish *regions* of additivity from *regions* of non-additivity, but only regions of a response (which is assumed to be additive) from a region of background response. According to the model, single chemical data is used to construct a prediction of what the response to a mixture of the chemicals would be if the response is additive, i.e. an assumption of additivity is made (page 199, first full paragraph, states "...the purpose of this report is to develop a flexible threshold model for the mixture(s) of interest *under the assumption of additivity*". Thus, the model is denominated the "threshold *additivity* model"(see formula 1.1 and next to last sentence of second paragraph of page 201).

As described in Gennings 1997, the threshold additivity model may be used to distinguish responses which are additive from responses which are not additive, but only at single points, i.e. at one specified mixture of agents at a time, not for an entire response surface. The last paragraph

of page 199 states: "We propose to construct a threshold additivity model that can be used to predict a response at *each combination of interest*. The observed response *at these combination points* can then be compared to that predicted under the assumption of additivity". Thus, at one combination of interest at a time, the predicted additive response is compared to an experimentally measured response at that combination. If the two are the same (i.e., not found to be statistically different), then the response is indeed claimed to be additive. If the two differ, then the response is not additive. Two possible deviations from additivity are possible: the response may be greater than that which the threshold additivity model predicts, in which case the chemicals are somehow interacting to increase the response (a synergistic relationship). Alternatively, the response may be less than that which is predicted by the threshold additivity model, in which case the chemicals are somehow interacting to decrease the response. This is clearly explained in the third full paragraph of page 199.

Applicant notes that nowhere in the analysis of Gennings 1997 is there a reference to regions of additivity and regions of interaction in dose space, or to the boundaries that separate such regions, or to "interaction threshold boundaries", as recited in claim 14.

One major difference between Gennings 1997 and the present invention is that for the "threshold additivity model"of Gennings 1997, the availability of single chemical data is required. This is described, for example, on page 199, in the first full paragraph which states " ...the purpose of this report is to develop a flexible threshold model... [which] only requires support from single-chemical concentration-effect curves..."; and the second full paragraph of page 199, which states: "The support of such a model is from *single-chemical dose-response data*...For example, data from different chemicals and historical studies can be combined to describe additivity"; and also in the last paragraph of page 199, which states "Suppose that we are interested in studying the interaction among *c* chemicals in combination, *where dose-response information is available on each single chemical.*"

In contrast, for the present invention as recited in claims 14 and 23, single chemical data is not required. If available, single chemical data may be used (see claims 15 and 19), but is not a requirement.

Applicant notes that the threshold additivity model of Gennings 1997, while useful, is highly limited in its application. Firstly, as shown above, the use of the model requires that single

chemical data be available for all chemicals in a mixture of interest in order to establish a prediction of additivity. Second, comparisons are made one mixture data point at a time. This is described in the paragraph above, and is illustrated in the Example provided in the paper, which begins on page 206. This example deals with four chemicals which are formed as disinfection by-products of water chlorination. The experimental animals were tested either for their response to increasing levels of a single chemical, or to one mixture of known, relevant proportions, "x" (see page 208, third paragraph). The single chemical data used to establish the prediction of additivity are presented in Table 1. The threshold additivity model used the single chemical data to predict the response to a mixture "x" and the result was compared to actual results obtained with "x". The results showed that "...the observed mean response was included in the prediction interval. Therefore, these data provide no evidence of departure from additivity at the combination point of interest" (lines 5-6 on page 210). Applicant notes that the threshold additivity model was not used to locate or predict interaction threshold boundaries between regions of additivity and regions of non-additive interaction for a mixture of chemicals.

The Examiner states that Gennings 1997 teaches a threshold additivity model for the purpose of analyzing groups of mixtures. Applicant notes that, as demonstrated above, a "threshold additivity model" is not the same as an "interaction threshold model". Further, Examiner's statement that the results of such an analysis are plotted in Figure 1 is incorrect. Figure 1 is a graphical representation of hypothetical additive data only. Figure 1 is provided as a visual aid to illustrate the simple concept that there are combinations of chemical mixtures at which the concentrations are so low that no measurable response is observed in a subject to whom the agents are administered, and that those "no response" concentration levels may change in the presence of other chemicals. In Figure 1a, the sections of the graph that are coincident with the x-y plane (i.e. where z=0) illustrate such combination of chemicals 1 and 2. However, if other agents are added to those same combinations, the concentrations of the mixtures of chemicals 1 and 2 at which a response is observed may be lower, i.e. less of chemicals 1 and 2 need to be administered to observe a response y. As can be seen in Figure 1b, for this theoretical instance, the area of the graph where z=0 is smaller, i.e. lower concentrations of the mixture of chemicals 1 and 2 elicit response z.

Applicant notes that this graph illustrates only additive relationships among the chemicals, and the purpose of the graph is to illustrate that the threshold at which a response can be detected (the line at which the planar surface begins to "bend" upward away from the x-y plane in the z direction) on the presence of additional chemicals. In this theoretical example, a non-additive relationship would cause the response surface where $z \neq 0$ to be non-planar. While the threshold additivity model of Gennings 1997 could be used to analyze single points on the surface one at a time, and determine whether or not they were consistent with the assumption of additivity represented in the graph (is the point on, below or above the surface?) it could not go further in the analysis of the entire response surface as does the interaction threshold model of the present invention.

The interaction threshold model of the present invention is capable of fitting data obtained with or without single chemical data to generate a generalized linear or a general nonlinear model that permits estimation of the boundaries between an entire region (not a point) of additivity and a region (not a point) of interaction (i.e. non-additivity) of the agents in a mixture (see claim 14). The establishment of such a model allows the prediction of other outcomes consistent with the model that would be caused by exposure to other combinations of the agents being considered, without actually doing the experiments (again, see claim 14).

Claim 14 has hereby been amended to recite that the region of interaction recited therein is a region of non-additive interaction. Support for this amendment is found in the specification as discussed above, e.g. in the first sentence of Example 8. Thus, this amendment does not add any new matter.

In summary, Gennings 1997 does not anticipate the present invention as recited in claim 14. Gennings describes a threshold additivity model which is distinct from the interaction threshold model of the present invention, and which cannot be used to perform the same types of analyses as can the interaction threshold model of the present invention.

In view of the foregoing, Applicant respectfully requests reconsideration of claim 14 and withdrawal of this rejection.

Claim Rejections: 35 USC § 103(a)

Gennings

Claims 1-26 and 30-31 stand rejected under 35 USC § 103(a) as unpatentable over Gennings et al. ((hereafter "Gennings 1998", *Journal of Agriculture, Biological and Environmental Statistics*, 1998, vol. 3, pages 1-16), in view of Gennings (1997) as above. This rejection is traversed.

Gennings 1998 also describes the use of a threshold model for binary data supported by a full ray design, and the inferences that can be drawn from the use of such a model. According to Gennings 1998, single chemical data is used to determine an additivity model. Specifically, single chemical data obtained with DEHP alone, HEPT alone and TCE alone. The predictions of additivity models generated from this data was then compared to data obtained using a mixture of the chemicals at various total doses, but held at the same ratios (70:1:29) within each mixture that was tried (i.e. full ray data).

As stated by the Examiner, Gennings 1998 "fails to teach that when the subsets of two agents are removed, the remaining agents (plural) must maintain their relative ratios". In other words, Gennings 1998 fails to teach the use of full and reduced rays. However, the Examiner then incorrectly contends that Gennings 1997 illustrates this in Figures 1a and b. Further, the Examiner appears to have overlooked the remaining steps of the method of claim 1, which are also not supplied by Gennings 1997. Claim 1 of the present invention does not simply require forming a subset, but then further testing the chemicals in the subset, and then carrying out a statistical analysis of the data in comparison to full ray data and/or data obtained with other reduced ray combinations.

Figures1a and b of Gennings 1997 are discussed above in the section discussing the 102 rejection. As can be seen from that discussion, Figures 1a and b serve as a visual aid to illustrate an extraordinarily simple principle. Figure 1 of Gennings 1997 illustrates, hypothetically, the regions of dose space that represent a background response (i.e. no response) compared to regions that represent a response (i.e., other than background). In Figures 1a and b, the "data" is hypothetical and simple addition was used to generate all points on the graph. No mathematical analysis of the data was performed or described, and the identification of the threshold response was purely visual. Steps such as those required in claim 1 of the application, (i.e., step d)

removing at least one subset of agents from said group or mixture, wherein relative ratios of amounts of remaining agents stay the same as in said fixed-ratio ray design; e) repeating steps b and c for agents remaining in said group or mixture after removal of said subset; and f) determining whether or not said remaining agents interact with said subset of agents by utilizing statistical hypothesis testing of said full and reduced ray mixture models, in order to detect, characterize or predict an outcome caused by exposure to said agents in said group or mixture) were not taught by Gennings 1997. Figure 1a and b only illustrate to the reader an already well recognized phenomenon: when additional agents are added to a mixture of chemicals, an effect of the mixture of chemicals is sometimes detected at lower doses than would be the case if the additional agents had not been added, i.e. the "threshold" dose at which the effect is observed changes. Figures 1a and b illustrate the case where the threshold dose is lowered, but could have as easily illustrated the case where the threshold dose is increased. No statistical analysis is provided, and no steps of relating full and reduced ray results to each other to detect, characterize or predict an outcome caused by exposure to the agents in the mixture (e.g. to determine departures from additivity, or to identify which agents interact, etc.). Thus, contrary to Examiner's assertion, these figures do not provide what Examiner contends is the missing teaching of Gennings 1998 that could be added to result in the present invention, and in no way supplies the steps of the method of claim 1 that Examiner has not taken into account.

Applicant herewith submits a declaration by an expert in the field of toxicology. The declaration is unsigned; a signed copy of the declaration will be filed shortly. The declaration establishes that there has been a long-felt need in the field for the type of analysis that is provided by the present invention, and that the long-felt need had not been satisfied even several years after the publication of Gennings 1997 and Gennings 1998. The declaration includes two authoritative and peer-reviewed references (Teuschler et al., 2002 and Monosson 2005), descriptions of the content of the two references, and a discussion of how each reference demonstrates that the long-felt need met by the present invention had not been met by Gennings 1997 and Gennings 1998, and was not obvious in view of the two references. Briefly, Teuschler et al. emphasize the need for new methods ("new" after 2002) to assess drug/chemical agent interactions in the absence of exhaustive, factorial data. Monosson establishes that the assessment of adverse health effects is largely based on a default assumption of no interaction,

even while acknowledging that this assumption may be incorrect, and that subthreshold exposures may cause adverse health effects. Applicant submits that neither Gennings 1997 nor Gennings 1998, nor any combination thereof, meets the needs described although both references had been publically available for several years prior to the publication of Teuschler and Monosson.

In addition, Applicant notes that Examiner has included claim 14 and all its dependent claims in this rejection, yet claim 14 recites a method that involves determination of an interaction threshold boundary, a concept that is not discussed or alluded to in either Gennings 1997 or Gennings 1998. Further, the point of rejection relied on by the Examiner (i.e. subsets) does not apply at least to claims 14-16, 19-20, 23-24 and 26, as there is no step involving subsets in any of those claims.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of this rejection.

Concluding Remarks

In summary, the primary reference applied by the Examiner (Gennings 1997) does NOT anticipate or render obvious the subject matter of the claims in the present application, unique features of which include:

the statistical analysis of subsets of the chemicals in a group (e.g. claim 1) and determination of an interaction threshold boundary (e.g. claim 14).

Further, Gennings 1998 does not cure the defective teaching of Gennings 1997.

In view of the foregoing, it is requested that the application be reconsidered, that claims 1-26 and 30-31 be allowed, and that the application be passed to issue.

Should the Examiner find the application to be other than in condition for allowance, the Examiner is requested to contact the undersigned at 703-787-9400 (fax: 703-787-7557; email: ruth@wcc-ip.com) to discuss any other changes deemed necessary in a telephonic or personal interview.

If an extension of time is required for this response to be considered as being timely filed, a conditional petition is hereby made for such extension of time. Please charge any deficiencies in fees and credit any overpayment of fees to Attorney's Deposit Account No. 50-2041.

Respectfully submitted,

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